



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/14, 9/72	A1	(11) International Publication Number: WO 99/34778 (43) International Publication Date: 15 July 1999 (15.07.99)
(21) International Application Number: PCT/FI98/01001 (22) International Filing Date: 21 December 1998 (21.12.98) (30) Priority Data: 974664 31 December 1997 (31.12.97) FI (71) Applicant (for all designated States except US): LEIRAS OY [FI/FI]; Pansiontie 45-47, FIN-20210 Turku (FI). (72) Inventor; and (75) Inventor/Applicant (for US only): LANKINEN, Tapio [FI/FI]; Jalustinkatu 11, FIN-20800 Turku (FI). (74) Agent: LEITZINGER OY; Ruoholahdenkatu 8, FIN-00180 Helsinki (FI).		(81) Designated States: AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: A METHOD FOR MAKING A PHARMACEUTICAL FORMULATION (57) Abstract The invention concerns a method for preparing a physically stable and homogenous powdered preparation containing in particulated form an active agent and optionally conventional physiologically acceptable additives, such as a carrier. The particles are suspended in a suspending agent, and from the thus obtained suspension the suspending agent is evaporated.		

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A method for making a pharmaceutical formulation

This invention concerns a method for preparing a physically stable and homogenous powdered preparation containing in particulated form an active agent and optionally conventional physiologically acceptable additives, such as a carrier.

Powder inhalers are widely used for ozone-saving dosing of active drugs into the lungs. These devices can be divided in two categories:

1. Devices provided with a powder reservoir and means for metering a dose from the reservoir for each delivery to the patient
2. Devices provided with pre-metered powder doses in capsules, blisters etc.

The performance of any powder inhaler must fulfill the requirements of Pharmacopeias for delivered dose uniformity ($\pm 25\%$ of mean). Also the mass of respirable particles per dose and general stability of the formulation must be documented and accepted by the authorities.

Concerning inhalation, the respirable particles are commonly accepted to be particles having an aerodynamic diameter less than 6 microns, which can be tested in laboratory.

Dry powders for inhalation are normally manufactured of micron size drug particles and a coarser carrier, e.g. lactose or glucose, by mixing them in a dry homogenizer. All micron size particles are very cohesive and tend to adhere strongly to each other and other surfaces (carrier, container etc.). Therefore, special care must be paid in the mixing process in order to obtain a homogeneous blend. Unhomogeneous blend will cause variations in the delivered dose, especially with reservoir devices, which additionally show a natural variation in accuracy of metering the dose.

When a dose is inhaled, a part of the micron size drug particles is separated from the carrier. Only these small deposit in the lung. If the forces adhering the drug particles onto other drug particles or carrier particles is increased, the amount of respirable particles will decrease and the clinical effect will be different. Altered adhesion also affects dose metering accuracy in reservoir devices.

A common reason for agglomeration of an inhalation powder is that some substances, often the drug, are in an unstable state. Such instability is mainly caused by polymorphic crystals or amorphous matter, which tend to recrystallize in a thermodynamically most stable state. Simultaneously, micron size particles tend to fuse together and adhere on any available surfaces. Such changes take place slowly at normal room circumstances but are commonly accelerated by elevated temperature, presence of moisture or organic vapours.

Polymorphic crystals may form during crystallization but a proper choice of the solvent may prevent it. Amorphous material is normally formed during high-energy treatment of organic solids, e.g. micronization in a jet-mill or ball-mill, or in rapid precipitation with anti-solvent or during spray-drying. Carried substances may contain amorphous matter as well.

As a summary, a manufacturing method resulting in excellent homogeneity of physically stable substances is well established.

The presence and characteristics of amorphous matter in micronized drug particles has been shown in several publications (e.g. with salbutamol by Ward and Schulz in Pharmaceutical Research, Vol. 12, No. 5, 1995).

In WO 95/05805 a micronized drug or a mixture containing micronized drug is stabilized by using water vapour preferably at 10-50°C and over 75 % relative humidity. This method is useful for water soluble substances. If the mixture contains water insoluble substances, vapour treatment with organic solvents should be carried out, too. Stabilization of dry powder is made by vapour and no wet suspension is mentioned. The authors suppose that, as a rule, water

soluble substances must be treated with water vapour and water insoluble substances with organic vapour.

- 5 In PCT/SE92/00186 a micronized water soluble drug is stabilized in similar manner with ethanol, acetone or other organic vapours. Prior to the treatment all water was removed from the drug at elevated temperature and under vacuum. After the treatment residues of organic solvent were removed from the drug with an inert gas. No suspension treatment is mentioned.
- 10 There are some drawbacks in treating dry powders. During vapour stabilization, the particles obviously tend to fuse together to some extent, which must be controlled. Adequate care must be paid to prevent contamination of drug during the treatment.
- 15 Suspension of an active drug in a volatile solvent in making a powder for inhalation is mentioned in U.S. patent 5,503,869. Here only micronized drug is suspended in HFA-propellants in order to fix an exact dose on a carrier net of metal, plastic, ceramic or similar material. When the propellant is evaporated, the drug can be blown into the air to be inhaled. No stabilization of the drug is
- 20 mentioned.

To overcome the drawbacks of the prior art the present invention provides a method for preparing a stable and homogenous dry particulated product which method is characterized in that the particles are suspended in a suspending

25 agent, and from the thus obtained suspension the suspending agent is evaporated

The other characteristics of the method of this invention are revealed in the claims 2 - 13.

30

The invention also concerns the product obtained by the method of this invention. The product is stable for longer periods and the particulate material is homogenous.

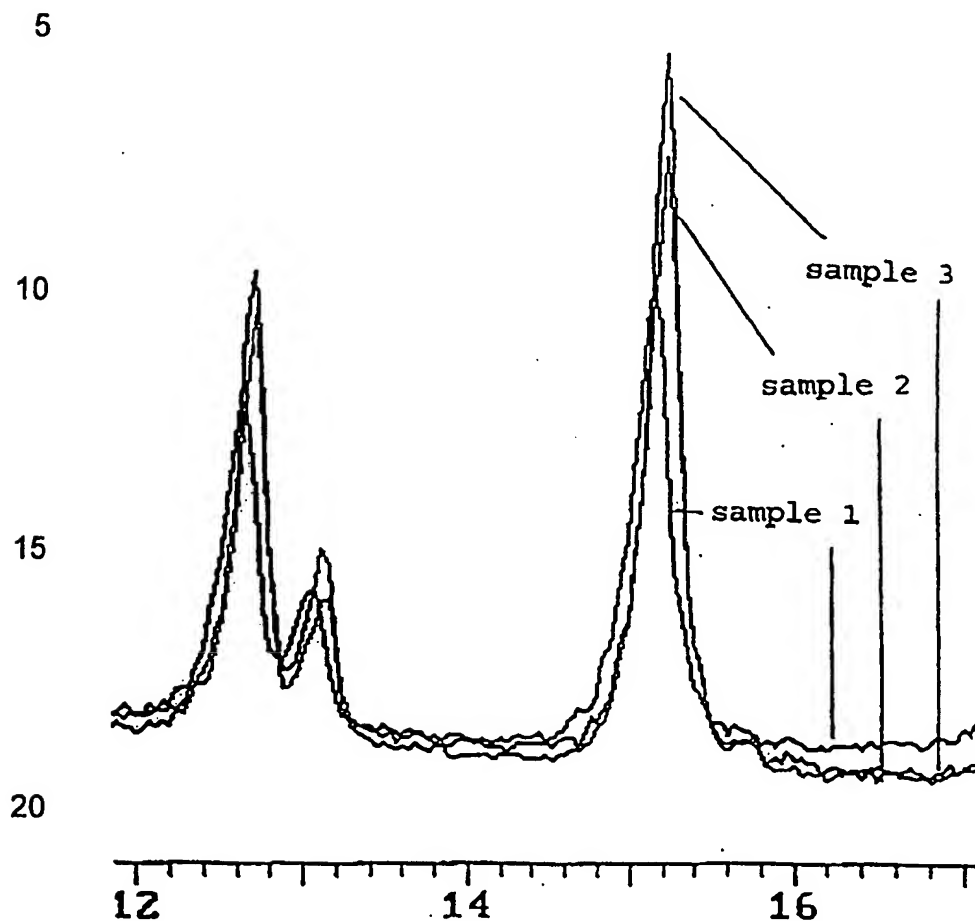
- Attempts to manufacture a lactose blend containing only 0,5 percents of an active drug by dry mixing failed because it was not possible to obtain a totally homogenous mixture of the ingredients by dry-mixing. It was found that the formulation always contained some agglomerates of the active drug, which spoiled the delivered dose uniformity in a reservoir powder inhaler. However, by mixing the ingredients as a n-heptane suspension aided by sonic treatment, a totally homogeneous blend was obtained after evaporation of heptane on a water bath.
- 10 When this method was used to make a formulation of salbutamol sulphate and lactose, a homogenous formulation was obtained, but its stability was not satisfactory; the drug particles agglomerated to an unacceptable level at room circumstances during six months.
- 15 One test formulation was left at room temperature as heptane suspension over weekend in a glass bottle, followed by evaporation of heptane on a water bath. Surprisingly, it was found later that this formulation remained stable for over two years at room circumstances. Apparently the prolonged suspension state stabilized the formulation probably due to physical changes in the active substance.
- 20

Example 1

Tests with salbutamol sulphate

- 25 Three samples of micronized salbutamol sulphate were stirred 7 hours at 50, 60 and 70°C as n-heptane suspension. Then the solvent was evaporated in vacuum.
- 30 Röntgendiffraction (XRD) studies suggested that a detectable amount of the drug was amorphous in the untreated sample but could be recrystallized during the treatment. Seven hours at 60 and 70°C resulted in practically total crystallinity and slightly less at 50°C.

When a sample of micronized drug was stored 100 hours at 40°C and 50 % relative humidity (RH), a clear decrease took place in the amount of amorphous matter. XRD patterns of three samples are shown below.



25 XRD patterns of three salbutamol samples

1 = micronized

2 = stored 100 hours at 40°C, 50 % RH

3 = stirred 7 hours at 70°C as n-heptane suspension.

30

Microcalorimetric (IMC) studies verified good stability of the treated samples in presence of moisture. The untreated sample was clearly unstable, especially at a RH of over 50 %.

Example 2

Preparing a salbutamol formulation

- 5 Micronized salbutamol sulphate was suspended in n-hexane to a thin slurry, aided by gentle sonic treatment at room temperature. Lactose (325 mesh) was added during mechanical stirring. The suspension was stirred some hours at 50°C, followed by evaporation of the solvent in a rotating evaporator. The resulting well-flowing powder was the ready formulation.

10

Homogeneity of the drug in the formulation was extremely good, showing RSD values for 2 mg samples of only 1-3%.

15

Characteristics for this formulation, when used with a model reservoir device, are:

- | | |
|---------------------------------------|----------------|
| Respirable fraction in delivered dose | 0,4 - 0,6 |
| RSD % for delivered dose uniformity | < 10 |
| Stability at room circumstances | over 2 years |
| 20 Stability at 40°C/75 % RH | over 1/2 years |

The characteristics are repeatable from batch to batch and the method has been scaled up for production.

25 Example 3

Tests with the experimental steroid A

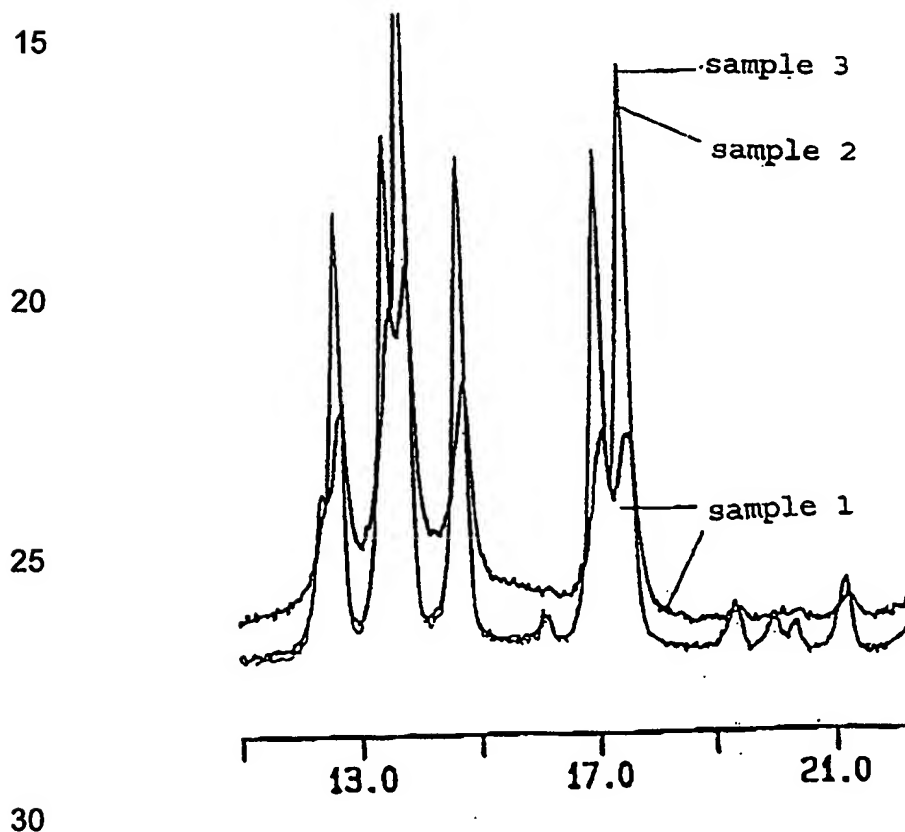
- 30 Attempts to make a lactose blend of a n-hexane suspension method at room temperature failed because particle size of the active drug in the delivered dose increased within weeks to an unacceptable level.

XRD studies suggested large differences in micronized and unmiconized materials, obviously due to different amorphous contents.

Freshly micronized drug showed no sharp diffraction patterns which indicates very high amorphous content. When stored at room circumstances for some months, a considerable fraction of the amorphous matter had been recrystallized. Also the initial mean particle size had been increased close to the upper acceptable limit.

Samples of some months ago micronized material were suspended in n-heptane and stirred 7 and 16 hours at 70°C, followed by drying. XRD- and IMC-studies confirmed total recrystallization of both samples.

XRD patterns of three samples are shown below.



XRD patterns of three samples of Steroid A

1 = micronized

2 = stored 100 hours at 40°C, 50 % RH

3 = stirred 7 hours at 70°C, as n-heptane suspension.

5 Example 4

Preparing a formulation of Steroid A:

10 The suspension of the drug in n-heptane was stirred 16 hours at 70°C. Then
lactose was added during stirring. The solvent was removed in vacuum in a
rotatory evaporator. As a result, free flowing dry powder was obtained. Stability
of the formulation was studied at extreme circumstances (40°C/75 % RH) by
metering the small particle fraction in the delivered dose, when the model
15 reservoir device was used. No change in the particle size distribution or
respirable fraction in the delivered dose could be seen, when tested after 2 and
4 weeks. The results indicate superb stability of the formulation compared to
earlier attempts with untreated micronized drug.

Example 5

20

Tests with the experimental Steroid B:

Four samples of micronized drug were treated in heptane-ethanol (96:4) and
dried:

25

1. mixing 30 minutes at room temperature
2. mixing 7 hours at room temperature
3. mixing 30 minutes at 50°C
4. mixing 7 hours at 50°C

30

XRD-studies revealed no large differences between the samples. However, the
untreated drug showed lowest peak height which suggests largest amorphous
content. Specific surface area and the energy for moisture absorption during
transfer from 0 to 80 % RH were metered:

		Area m ² /g	ΔH J/m ²
	Micronized, untreated	6,55	1,21
	Sample 1	6,17	0,95
	2	5,30	0,99
5	3	5,69	0,94
	4	5,38	1,00

The differences are small but indicate that a physical change took place during the treatment and the treated samples are in a more stable state compared to the untreated sample. The overall results encourage to use suspension stabilization using short treatment at normal or slightly elevated temperature.

Further experiences and clarifications on the method

Budesonide and three experimental drugs for inhalation have been formulated using the suspension mixing method. Coarse lactose or glucose was used as the carrier and the drug-carrier ratios varied between 1:200 and 50:100. N-alkane alone or mixed with a small amount of ethanol or methanol was used as suspending agent. In all cases short mixing times were used, followed by removal of the suspending agent in a rotating evaporator. Budesonide formulation showed excellent homogeneity and stability; no changes in the particle parameters have been found at room circumstances within one year.

The formulations of the three experimental drugs showed excellent homogeneity and acceptable stability.

The suspending method is a very useful method for homogenizing, even if all of the ingredients were in a stable state. If not stable, it is easy to increase the mixing time and/or mixing temperature and monitor the results by physical methods instead of timely stability tests. During this stabilization, the essential benefit of the suspension method is that the liquid prevents agglomeration of the particles during recrystallization.

The manufacturing process can be done in a totally closed system in absence of water. The process is very safe in respect to any contamination and can be used in large-scale production. The mixing vessel can be equipped with mechanical stirrer, ultrasonic transmitter, heating and filtering means and vacuum evaporation so that the formulation is ready to use after the process.

There seems to be no other limitations concerning the suspending agent, but it must be chemically inert in respect of the formulation components, fairly volatile and the components must be practically insoluble in the suspending agent.

10 N-alkanes are ideal in most cases. Small amounts of methanol, ethanol, acetone etc. may be used to improve wetting of the powders. Even absolute ethanol and halogenated hydrocarbons, such as CFC 11 and HFC 227, have been used successfully in making a salbutamol sulphate - lactose monohydrate formulation.

15

If heat treatment is used, it can be conducted separately for the drug and the carrier or jointly for the drug, carrier and other possible ingredients concerned. It is preferred to treat both the drug and the carrier, because also the carrier may contain unstable matter and cause formulation changes during storage.

20 As shown with salbutamol, some hours mixing in n-hexane at 50°C will produce a practically stable formulation.

Claims

1. A method for preparing a physically stable and homogenous powdered preparation containing in particulated form an active agent and optionally conventional physiologically acceptable additives, such as a carrier, **characterized** in that the particles are suspended in a suspending agent, in which the particles are essentially insoluble in the suspending agent, and from the thus obtained suspension the suspending agent is evaporated.
2. A method according to claim 1, **characterized** in that the suspending agent is selected from alkanes, alcohols, ketones or mixtures thereof.
3. A method according to claim 2, **characterized** in that the suspending agent is selected from an alkane, preferably n-hexane or heptane, an alcohol, preferably methanol or ethanol, and a halogenated hydrocarbon.
4. A method according to any of claims 1 - 3, **characterized** in that the suspended particles are deagglomerated and/or homogenized by mechanical stirring.
5. A method according to any of claims 1 - 4, **characterized** in that the suspension is subjected to sonic treatment.
6. A method according to any of claims 1 - 5, **characterized** in that the suspension is maintained for a while to allow contact between the particles and the suspending agent before evaporation.
7. A method according to claim 6, **characterized** in that the suspension is maintained for a time of a few minutes to several days, preferably some hours.
8. A method according to any of claims 1 - 7, **characterized** in that the method is conducted at elevated temperature.

9. A method according to claim 9, **characterized** in that the temperature is between about 40 - about 90°C, preferably about 40 - about 70°C and most preferably 50 - 70°C.

5 10. A method according to any of claims 1 - 9, **characterized** in that the active agent is an organic compound containing amorphous substance.

11. A method according to any of claims 1 - 10, **characterized** in that the active agent is salbutamol.

10

12. A method according to any of claims 1 - 10, **characterized** in that the active agent is a steroid.

13. A method according to claim 13, **characterized** in that the active agent is
15 budesonide.

14. A product obtained by a method according to any of the claims 1 - 13.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 98/01001

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/14, A61K 9/72

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, CAPLUS, USPATFULL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	GB 937303 A (BENGER LABORATORIES LIMITED), 18 Sept 1963 (18.09.63), page 2, line 102 - page 3, line 30, claims --	1-14
A	WO 9505805 A1 (ASTRA AKTIEBOLAG), 2 March 1995 (02.03.95), claims -- -----	1-14

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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Date of the actual completion of the international search

16 April 1999

Date of mailing of the international search report

29-04-1999

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INTERNATIONAL SEARCH REPORT

Information on patent family members

02/03/99

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